Current development and Evaluation of Vaccine & Safety & Efficacy Evaluation of Vaccines

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KFDA's Biologics Headquarters is responsible for regulating vaccines, blood products, biotechnology derived products, human stem cell therapies, gene therapies, allergenic materials and anti-toxins in Korea. Current authority for the regulation of Biologics resides primarily in Section 26 34 of the Pharmaceutical Affairs Act.

Vaccines are relatively new and powerful weapons against infectious disease. Ever since Edward Jenner's first experiments with cowpox and smallpox in 1796, humans have been using technology to enhance the immune system and combat the worst infectious diseases. Vaccines have controlled formerly wide spread infections like pertussis, diphtheria and meningitis due to *Haemophilus influenza* and nearly eliminated measles and polio. Although humans still fight disease every day, vaccines have given us the upper hand against these and other major diseases.

Vaccines are classified into 2 types; the inactivated (or killed) vaccine and the live attenuated vaccine. With the accumulating knowledge on protective antigens, it is possible to construct more effective component vaccines but the cost for development would be high. Besides, the efficacy of inactivated vaccines or component vaccines is lower than a live vaccine in general. Live vaccines are inexpensive and the protective effect is persistent, but there is a risk for reversion in the virulence. Development of live vaccines has advantages and disadvantages. Therefore, the future direction of vaccine development will not be restricted as one of the two. However, the search for component vaccines will certainly become predominant in the future. Multivalent vaccines, which cover 2 or more individual vaccination at once, are desired.

Construction of a recombinant vaccine by a molecular engineering technology to combine the DNA of a protective antigen and an attenuated virus may become practical in the near future. Use of adjuvant and studies on drug-delivery systems will improve the efficacy of vaccines. Heat-stable or heat-resistant vaccines are required in the tropical areas. Ideal routes of administration for the future vaccines are oral and intranasal. Until recently, all licensed vaccines were developed using conventional technologies. However, the introduction of modern molecular biological tools and genomics, combined with a better understanding of not only which antigens are critical in inducing protection, but an appreciation of host defenses that must be stimulated, has opened a new

opportunity to develop safer and more effective vaccines. The speaker presents the current and future trends in vaccine development and stress that in addition to identifying and producing the protective antigen, it is critical to formulate and deliver these vaccines appropriately to maximize the potential of modern advances in pathogenesis and vaccinology.

Vaccine clinical development follows the same general pathway as for drugs and other biologics A sponsor who wishes to begin clinical trials with a vaccine must submit an Investigational New Drug application (IND) to KFDA. The IND describes the vaccine, its method of manufacture, a description of the drug substance including its physical, chemical or biological characteristics, specification and information to support the stability etc. Also included are information about the vaccine's safety and ability to elicit a protective immune response (immunogenicity) in animal testing, as well as the proposed clinical protocol for studies in humans.

Pre-marketing (pre-licensure) vaccine clinical trials are typically done in three phases, as is the case for any drug or biologic. Initial human studies, referred to as Phase 1, are safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase 2 studies are dose-ranging studies and may enroll hundreds of subjects. Finally, Phase 3 trials typically enroll thousands of individuals and provide the critical documentation of effectiveness and important additional safety data required for licensing. At any stage of the clinical or animal studies, if data raise significant concerns about either safety or effectiveness, KFDA may request additional information or studies, or may halt ongoing clinical studies.

Current regulation, Guidance on IND application(Korea FDA regulation 2004-51, 2004.7.19), contains the general requirements for IND's content and format. In case of biologics including vaccines, the amount and depth of CMC information depends on the phase of the investigation. All the clinical investigations should be complied with Enforcement provision 29 and Good Clinical Practice(KFDA regulation 1999-67, 2000.1.4).

If successful, the completion of all three phases of clinical development can be followed by the submission of a Biologics License Application. To be considered, the license application of vaccines must provide the several KFDA review teams (Biologics review team, Viral Vaccine Team(in case of viral vaccine), Bacterial Vaccine Team(in case of bacterial vaccine)). Also during this stage, we conduct GCP, GMP inspection. If necessary, we consult the central Pharmaceutical Affairs Council.

Vaccine approval also requires the provision of adequate product labeling to allow health care providers to understand the vaccine's proper use, including its potential benefits and risks, to communicate with patients and parents, and to safely deliver the vaccine to the public.

Until a vaccine is given to the general population, all potential adverse events cannot be anticipated. Thus, many vaccines undergo phase 4 studies for re examination.